Osteoporosis and Vitamin D Deficiency in Patients with Sickle Cell Disease

Orak Hücre Anemili Hastalarda Vitamin D Eksikliği ve Osteoporoz

Osteoporosis in Sickle Cell Anemia

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Özet

Amaç: Osteopeni veya osteoporoz gibi kemik hastalıkları orak hücre hastalığında (OHA) en sık görülen ve morbidite nedeni olan klinik bulgulardandır. D vitamini eksikliği de dahil olmak üzere, kemik problemlerinin oluşumunda birçok neden vardır. Bu çalışmada; kemik mineral dansitometrisi (KMD) ve biyokimyasal endeksleri kullanarak OHA hastalarında osteopatiyi değerlendirmeyi amaçladık. Gereç ve Yöntem: Bu çalışmaya 29 kadın, 32 erkekten oluşan toplam 61 hasta dahil edildi. Yaş, cinsiyet, biyokimyasal parametreler ile dual enerji X ışını absorpsiyometri kullanılarak (DEXA) lomber vertebralarda KMD düzeyi değerlendirildi. Z skorlarına göre; <[-2] osteoporoz, [-1/-2] osteopeni, >[-1] normal olarak kabul edildi. Çok değişkenli analiz yöntemi ile de KMD'yi etkileyen faktörler belirlendi. Bulgular: 61 hastanın yaş ortalaması 21.06±5.06 (15-27) yıl idi ve vücut kitle indeksi (VKİ) 19.15±2.98 kg/m2 olarak hesaplandı. 23 hasta (11 kadın, 12 erkek) (%37.7) osteopenik iken 26 hasta (12 kadın, 13 erkek) (%44.3) osteoporotik idi. 12 hastanın (6 kadın ve 6 erkek) (% 18) KMD'si normal sınırlarda saptandı. D vitamini 12 hastada (%19.67) (10 kadın, 2 erkek) ciddi seviyede düşük bulunmuştur (<10 ng / ml). 20 hastada (% 32.8) (14 kadın, 6 erkek) D vitamini eksikliği (10-20 ng / ml) ve 26 hastada (% 42.6) (14 kadın, 12 erkek) ise yetersiz düzeyde (20-30 ng/ml) görülmüştür . Hemen hemen tüm kadınlarda (28/29) D vitamini düzeyleri düşük iken (20 ng/ml), 18/32 erkek hastada D vitamini eksikliği saptanmıştır. Lomber KMD yaş (p <0.001), boy (p <0.001), ağırlık (p <0.001), VKİ (p <0.001), Hb (p = 0.017), Z skoru (p <0.001) ile pozitif korele bulunmuştur. Tartışma: OHA hastalarında osteopati patogenezinde rol oynayan birçok gösterge vardır. Bu faktörler dikkate alınmalı; tanıda gecikilmemeli ve bu hastaların yaşam kalitesini artırmak için gerekli tedbirler alınmalıdır.

Anahtar Kelimeler

Osteoporoz; Orak Hücreli Hastalığı; Vitamin D Eksikliği

Abstract

Aim: Bone disorders such as osteopenia or osteoporosis are the most common clinical manifestations seen in sickle cell disease (SCD) with a high of morbidity. There are many reasons, including vitamin D deficiency for the appearance of bone problems. In the present study we aimed to evaluate osteopathy in patients with SCD using bone mineral densitometry (BMD) and biochemical indices. Material and Method: 61 patients (29 female, 32 male) were included in the study. The age, gender, and biochemical parameters with BMD were evaluated using dual energy X-ray absorptiometry from lumbar vertebrae. According to Z scores, [<-1] was normal, [-1/-2] was osteopenia, and [>-2] was considered as osteoporosis. Multivariate analysis was performed to determine the factors influencing BMD. Results: There were a total of 61 SCD patients. The average age was 21.06±5.06 (15-27) years and the mean BMI was 19.15±2.98 kg/m2. 23 patients were osteopenic (11 female, 12 male) (37.7%) and 26 were osteoporotic (12 female, 13 male) (44.3%). Twelve patients (6 female and 6 male) (18%) had normal Z scores. Vitamin D was found severely deficient (<10 ng/mL) in 12 patients (19.67%) (10 female, 2 male). Vitamin D was deficient (10-20 ng/mL) in 20 patients (32.8%) (14 female, 6 male) and insufficient (20-30 ng/mL) in 26 patients (42.6%) (14 female, 12 male). Almost all of the females (28 of 29) had vitamin D levels lower than 20 ng/mL and 18 of 32 males had deficiency. Lumbar BMD was positively correlated with age (p<0.001), height (p<0.001), weight (p<0.001), BMI (p<0.001), Hb (p=0.017), and Z score (p<0.001). Discussion: There are many indicators playing a role in the ethiopathogenesis of osteopathy in SCD patients. These factors should be considered, the diagnosis should not be delayed, and measures should be taken to improve the quality of life of these patients.

Keywords

Osteoporosis; Sickle Cell Disease; Vitamin D Deficiency

DOI: 10.4328/JCAM.4289 Received: 12.01.2016 Accepted: 02.02.2016 Printed: 01.07.2016 J Clin Anal Med 2016;7(4): 483-7
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Introduction

Sickle cell disease (SCD) is one of the most common hemoglobinopathies in the world. SCA carrier frequency is between 0.3-0.6 percent across Turkey; in some areas such as the Çukurova region, this frequency reaches up to 3.0-44.0%. Due to complications of this chronic inflammatory disease associated with chronic hemolysis, vasoocclusion, and tissue hypoxia, bone metabolism is adversely affected as are other endocrine organs [1]. Painful vaso-occlusive crisis or osteomyelitis is the acute clinical manifestations whereas osteonecrosis, osteoporosis, and osteopenia can be seen in the long term. Although morbidity remains high, survival of individuals with SCD to over the age of 55 or 60 has been described [2]. There are several studies on SCA adults that show they have lower bone mineral density (BMD) and lower vitamin D values than do healthy controls [3].

Osteopenia and osteoporosis have a frequency of up to 82% of adults with SCD [4, 5]. The ethiopathogenesis of osteoporosis and demineralization of bone in SCD seems to be multifactorial. Bone marrow expansion and cortical thinning, hypogonadism, hypothyroidism, hypoparathyroidism, direct toxic effects of iron overload on osteoblast numbers and activity, calcium and zinc deficiencies, low vitamin D levels, and reduced physical activity are some of the responsible acquired factors. Also, low body mass index (BMI) plays a role in the bone metabolism that can be connected to the hypermetabolic state in SCD. Chronic inflammatory processes, chronic anemia, increased cardiac load, rapid erythropoiesis, increased protein turnover, and oxidative stress all contribute to the hypermetabolic condition [6].

In these patients, vitamin D deficiency is very common in clinical practice. Defining deficiency as vitamin D <20ng/mL, deficiency is seen in from 56.4% up to 96.4% of SCD patients. Vitamin D seems to be a serious health problem around the world, not only because it affects bone metabolism [7]. Vitamin D deficiency has been shown to affect the prognosis of many diseases such as cardiovascular diseases, nephropathy, and chronic pain [8]. The vicious circle caused by all these complications reduces both the quality of life and the survival of SCA patients [9].

Osteopenia and osteoporosis are usually asymptomatic in clinical settings. If there are fracture deformities or vertebral collapse, patients complain of pain and are admitted to outpatient clinics. In those cases, chronic analgesia and mechanical/surgical support are usually needed. So we think that careful and accurate management of these patients will significantly increase their quality of life.

Material and Method

61 SCD patients who visited the outpatient clinic of the university hospital, ranging in age from 15-27, whose diagnoses were confirmed with hemoglobin (Hb) electrophoresis were asked to participate in the study. Ethical approval was obtained from the ethics committee of the university. Informed consent was obtained from all participants. Patients with secondary disorders that might cause osteoporosis were ruled out. Patients who did not receive regular treatment, who were on steroids, were using osteoporosis-preventive medicine (calcium and vitamin D) or therapeutic (bisphosphonates, etc.) agents, or had anorexia nervosa, hyperthyroidism, chronic obstructive pulmonary disease, or inflammatory bowel disease were excluded from the study.

Age, sex, and drugs with chelator agents were noted. Body mass index (BMI) was calculated. Before the transfusion, Hb, ferritin, fasting blood glucose (FBG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), Ca, phosphorus (P), alkaline phosphatase (ALP), thyroid stimulating hormone (TSH), free thyroxine (FT4), intact parathyroid hormone (iPTH) and vitamin D levels were measured. Bone mineral densities (BMD) of the patients were evaluated by the DEXA method. BMD of the lumbar spine (L1-L4) was measured in g / cm2. Z scores were calculated automatically by the device. Z score of [<-1] was defined as normal, [-1-2] as osteopenia and [> -2] as osteoporosis. The statistical analyses were carried out by Statistical Package for the Social Sciences (SPSS). Variables were expressed as mean±SD. Comparisons of variables were performed using unpaired Student t test. Bivariate associations of the variables were assessed using Pearson's correlation coefficients and p value <0.05 was considered to indicate statistical significance.

Results

There were a total of 61 SCA patients: 29 were female and 32 were male. The average age was 21.06±5.06 (15-27) years, height 152.09±17.61 cm and weight 45.69±14.29 kg. Mean BMI was 19.15±2.98 kg / m2.

Patients were grouped according to the lumbar region Z score, with [> -1] as normal, [-1 -2] as osteopenic and [<-2] as osteoporotic. With regard to Z scores, 23 patients were osteopenic (11 female, 12 male) (37.7%), 26 patients were osteoporotic (12 females, 13 males) (44.3%) and 12 patients (6 females and 6 males) (18.0%) had normal Z scores. The average data for all three groups are summarized in Table 1.

Table 1. Demographic features and laboratory findings of sickle cell anemia

	All patients N:61	Z score >-2 N:26	Z score -1- -2 N:23	Z score normal N:12
Age (year)	21.06±5.06	18.58±3.58	22.61±5.85	20.66±2.98
BMI (kg/m2)	19.15±2.98	18.34±2.95	20.47±2.40	19.33±3.06
glucose (mg/dL)	85.74±9.20	86.31±8.13	85.50±10.32	83.93±10.40
Hb (g/dL)	8.41±1.08	8.07±1.21	8.94±.71	8.48±0.81
ferritin (g/dL)	893.93±1566.34	967.44±1751.18	1146.50±1850.23	538.47±562.12
ALT (U/L)	28.18±28.23	24.87±11.75	40.68±51.77	22.06±10.70
AST (U/L)	43.79±17.69	45.34±13.83	46.93±25.01	38.50±15.10
ALP (U/L)	144.28±89.50	140.56±87.17	142.13±76.90	169.66±112.88
Ca (mg/dL)	9.51±0.76	9.40±.96	9.49±0.39	9.73±0.50
P (mg/dL)	4.43±.65	4.57±0.55	4.31±0.84	4.23±0.60
TSH (mIU/L)	3.90±8.38	3.10±1.20	2.53±1.15	6.89±16.95
Ft4 (ng/dL)	5.71±6.73	6.70±6.77	3.73±6.42	6.94±8.07
PTH (pg/mL)	76.07±175.17	89.00±216.26	83.36±110.49	81.40±125.67
Vit D (ng/mL)	19.78±9.52	19.83±5.78	19.74±17.47	19.40±10.73
B12	344.59±236.74	383.66±311.67	325.50±188.15	315.71±153.09
Folat	10.15±6.22	8.89±5.81	9.09±6.42	12.23±7.33
BMD (g/cm2)	0.72±0.23	0.59±.13	0.83±0.16	0.91±0.23
Z score	-1.84±1.66	-2.78±0.79	-1.48±0.23	0.52±1.37

BMI; body mass index, Hb; hemoglobin, ALT: alanine transaminase, AST; aspartate transaminase, Ca; calcium, P; phosphorus, TSH; thyroid stimulating hormone, Ft4; free thyroxine, PTH; parathyroid hormone, Vit D; vitamin D, BMD; bone mineral densitometry

6 female and 12 male had low BMI (<18.5 kg/m2). Osteoporosis was seen in 50% of females and 58% of males in this group. Low BMI was positively correlated with Z scores (p=0.043, r=0.457).

Vitamin D was found severely deficient (<10 ng/mL) in 12 patients (19.67%) (10 female, 2 male). Vitamin D was deficient (10-20 ng/mL) in 20 patients (32.8%) (14 female, 6 male). Vitamin D was insufficient (20-30 ng/mL) in 26 patients (42.6%) (14 female, 12 male). Almost all of the females (28 of 29) had vitamin D levels lower than 20 ng/mL and 18 of 32 males had deficiency.

Lumbar BMD was positively correlated with age (p<0.001), height (p<0.001), weight (p<0.001), BMI (p<0.001), Hb (p=0.017), and Z score (p<0.001) and negatively correlated with P (p=0.031) (Table 2).

The mean BMD in females was 0.79±0.25 and in males was 0.66±0.20. BMD values of males were lower than females and this was found statistically significant (p=0.042).

The mean vitamin D value of females was 17.17±7.5 and in males was 23.90±11.86. Although males had higher values than females, this was not statistically significant (p=0.062).

In the osteoporotic group, ALP was found higher in 13 patients (50.0%), AST in 15 patients (57.7%), ALT in 5 patients (19.2%), TSH in 1 patient (3.8%), FT4 in 11 patients (42.3%), P in 9 patients (34.6%). Ferritin was high in all patients. FBG, and Ca were normal in all, while vitamin D was severely deficient in 4 (15.3%), deficient in 10 (38.4%), and insufficient in 12 (46.3%). There were no normal vitamin D levels in this group.

In the osteopenic group, FBG, Ca, P, and TSH levels were all within normal limits. High values were found for ALP in 7 patients (30.4%), P in 7 patients (30.4%), PTH in 1 patient (4.3%), ALT in 3 (13.0%), AST in 14 (60.8%), and FT4 in 6 (26.0%). Vitamin D was severely deficient in 5 (21.7%), deficient in 5 (21.7%), insufficient in 10 (43.4%), and normal in 3 (13.2%).

Of those with Z scores in the normal range, vitamin D was severely deficient in 3 (27.6%), deficient in 4 (36.2%), insufficient in 2 (18.1%), and normal in 2 (18.1%)P was higher in 2 (18.0%), ALP in 5 (45.5%), ALT in 1 (9.0%), AST in 5 (45.5%), TSH in 3, and FT4 in 5 (45.5%). Ca and PTH values were within normal limits.

Discussion

Osteoporosis is the most common skeletal system disorder worldwide. It is characterized by reduced bone mass and disruption of bone architecture. Because this increases the risk of bone fragility and fractures, it is an important cause of morbidity in adult patients [10]. The prevalence of low BMD ranges from 30 to 82% in SCD [1, 4, and 5] for the lumbar spine. It has been shown that while bone metabolism, thyroidal disorders, or gonadal insufficiency as endocrine organ dysfunctions are more frequently seen in adult SCD patients, malnutrition, growth retardation, and pubertal development retardation are mostly seen in pediatric patients [9].

In the present study, 37.7% of SCA patients were found osteopenic and 44.3% as osteoporotic based on Z scores of the patients, according to WHO guidelines. Vitamin D was severely deficient in 12 patients (19.67%), deficient in 20 patients (32.8%) and insufficient in 26 patients. Lumbar BMD was positively correlated with age, BMI, Hb, and Z score.

60 adult SCA patients ranging in age from 20-40 had significantly lower BMD at L2, L4 (all p < 0,05) than the control group in the study of Elshal MF et al. [11]. 30% of the patients were osteopenic and 50% were osteoporotic. Furthermore, there was significant reduction in PTH and serum Ca concentrations. In our study all the calcium levels were normal. In the study of Sadat-Ali M et al [7], in a total of 100 SCA patients consisting of 48 males and 52 females, 70% had low bone mass (osteopenia and osteoporosis). In a study conducted in Brazil with 65 SCA patients, low BMD was present in 41% and a relationship was found between low BMD and hemolysis parameters such as high lactate dehydrogenase (LDH) and low hemoglobin level [12]. In a study of Sarrai M et al. [5] on 103 SCA patients (73 females, 30 males, aged 15-80 years), 79.6% (mean age 36.5±12.5 years) had low BMD. Abnormal BMD was related to

Table 2. Pearson's correlations between bone mineral densitometry and other laboratory parameters in children with sickle cell anemia

	BMD	age	BMI	Hb	ferritin	glucose	Ca	P	ALP	PTH	ALT	AST	TSH	Vit D	Z skor
BMD	1														
Age	,673**	1													
BMI	,564**	,533**	1												
Hb	,323*	,146	,345*	1											
Ferritin	-,230	-,183	-,054	-,278*	1										
glucose	-,153	-,015	-,245	-,301*	,398**	1									
Ca	,048	,170	,213	,096	,012	,125	1								
P	-,294*	-,530**	-,229	-,078	,013	-,066	,087	1							
ALP	-,145	-,194	-,269*	-,377**	,308*	,094	,097	,178	1						
PTH	-,138	,092	-,485*	-,493**	,851**	,320	,048	-,012	,827**	1					
ALT	,013	-,037	,092	,101	,397**	,005	,024	,253*	,066	,037**	1				
AST	-,202	-,154	-,169	-,189	,136	-,016	,059	,318*	,141	-,213	,698	1			
TSH	,108	-,052	,163	,054	-,018	-,018	,026	,062	-,034	-,077	-,016	-,023	1		
Vit D	,160	,093	,205	,254	,020	-,059	,188	,212	-,096	,151	,046	-,084	-,057	1	
Z skor	,660**	,259	,162	,214	-,064	,057	-,010	-,165	,048	-,211	-,005	-,111	,076	,037	1

**Correlation is significant at the .01 level (2-tailed). * Correlation is significant at the .05 level (2-tailed)

BMD: bone mineral densitometry, BMI: body mass index, Hb: hemoglobin, Ca: calcium, P: phosphor, ALP: Alkaline Phosphatase, ALT: alanine aminotrensferase, AST: aspartate aminotransferase, TSH: thyroid stimulating hormone, PTH: parathyroid hormone, vit D: vitamin D

lower body mass index (BMI) (p = 0.003), lower Hb level (p = 0.001) and higher ferritin (p = 0.003) but not correlated with age and sex. BMI, ferritin, and hemoglobin levels were the major role players for abnormal BMD in this study [5]. In another study on 17 SCA patients, osteopenia frequency was 47% and serum iron and ferritin levels were found higher in osteopenic patients than patients with normal BMD [13]. In the study of M. Meeuwes et al. [14] on 27 patients ranging in age from 7-28, low BMD was not correlated with age, gender, calcium, calorie intake, or laboratory measurements. Low BMD was present in 11 patients (4 females, 7 males). The mean BMD Z score was 1.81 SD in males and -0.80 SD in females. There was no relationship found between BMD and gender in children and young adults with SCA in the study of Buison et al. [3] and low BMD was seen more often in older boys. In the study of Redonda G et al. [4], of 32 adults with SCD (14 men and 18 women) with a mean age of 34 years, 72% (95% confidence interval 53–86%) had low BMD at one or more anatomic sites; 13 (40%) were osteoporotic and 10 were osteopenic. Decreased BMD was correlated with low BMI (p< 0.001) and male sex (p= 0.002).

While 25-hydroxyvitamin D levels are found to be lower in most of the studies in almost all of the patients, there are no significant associations between vitamin D and BMD. In a prospective study [15] consisting of 56 SCD adult patients (mean age 29.8±9.5 years), the median 25(OH)D concentration was 6 ng/ml; vitamin D deficiency (25(OH)D <10 ng/mL) was found in 42 (75.0%) and secondary hyperparathyroidism in 40 (71.4%). There was a history of fracture in 17 patients (30.3%), and osteopenia and/or osteoporosis in 39.6% of the patients. Goodman et al. [16] also reported 86% of their adult patients having vitamin D levels below 10 ng/mL. 139 of 142 (98%) had suboptimal levels (<30 ng/mL) and 85 of 142 (60%) had severely deficient vitamin D (<10 ng/mL). Vitamin D was not correlated with age, sex, or date of lab draw. Miller et al. [4] reported that 84% of patients had lower serum 25-hydroxyvitamin D concentrations (<20 ng/mL) and 66% had below 10 ng/mL, but low vitamin D concentration was not related to low BMD.

In the study of Sadat-Ali et al. [7] (86 males and 100 females), 92.0% of females and 70.9% of male patients with SCD had vitamin D deficiency. The prevalence of osteoporosis was found to be 73.8% (45/61) in males and 92.4% (85/92) in females. ALP and PTH were significantly higher but 25(OH) D levels were significantly lower. Lumbar spine BMD was positively correlated with age, serum calcium, and vitamin D levels and negatively correlated with PTH.

In the study of Özen et al. 17] consisting of 38 patients, 24 (63.1 %) had vitamin D deficiency, 7 (18.4%) had vitamin D insufficiency, and iPTH was found high in 18.4% (n=7/38). 3 patients (6.0%) were diagnosed with hypothyroidism (1 central, 2 primary hypothyroidism) in this study. PTH was higher in 3 of our patients (2 osteoporotic and 1 osteopenic).

As with many other systems, the hepatobiliary system is affected in SCD. The vascular obstruction and hemolysis can result in recurrent ischemia of the liver and bilirubin stones can occur [18]. The iron overload can also lead to liver dysfunction and fibrosis [19, 20]. Drugs taken by sickle cell patients may cause or worsen hepatobiliary disease. In general, AST is relatively more elevated than ALT due to hemolysis [21]. However, the elevation of ALT contributes more to hepatocellular damage than elevation of AST. Similarly, the alkaline phosphatase can be elevated in biliary diseases. However, bone infarcts can also raise the alkaline phosphatase levels. In our study, AST levels (14 patient in the osteopenic group, 15 in the osteoporotic group and 5 in the normal BMD group) were more frequently found higher than were ALT levels (3 patients in the osteopenic group, 5 in the osteoporotic group and 1 in the normal BMD group). ALP levels were found higher in 25 of 61 (7 patients in the osteopenic group, 13 in the osteoporotic group and 5 in the normal BMD group).

Clinical trials done in tropical countries that have a high incidence of SCD demonstrate that occurrence of either type 1 or type 2 diabetes is a rare finding [22]. The low BMI, hypermetabolism, and perhaps genetic factors may protect SCD patients from diabetes. A 5 year prospective study in Canada, the USA, and the UK reported that diabetes mellitus affects 2% of patients with SCD [23]. In our study glucose levels were normal for all patients.

Abnormal thyroid function tests have also been reported in patients with SCD. In the study of Parshad O et al. it was reported that male patients had significantly lower endogenous T3 and higher TSH levels [24]. The etiology of thyroid dysfunction in SCD is unclear. Iron deposition in the thyroid gland has been shown in autopsy reports, so the etiology might be due to transfusional hemosiderosis and cellular damage to the thyroid gland [25]. In the present study TSH was found high in 4 of the patients. Surprisingly, free T4 was high in 22 (6 patients in the osteopenic group, 11 in the osteoporotic group and 5 in the normal BMD group) but thyroid function tests were not correlated with BMD.

Conclusion

As the disease progresses the number of transfusions increases (more than eight per year). There is a resulting iron overload and greater risk of endocrine organ failure. During skeletal growth in childhood, starting adequate vitamin D and calcium intake, weight-bearing exercise, early diagnosis of hypogonadism or growth hormone deficiency, and preventing iron overload and its treatment are essential in the care of patients. After reaching patients at the age of expected peak bone mass, they should be screened for osteoporosis at least once a year (at least 2 separate sites using dual energy X-ray absorptiometry (DEXA)) and vitamin D levels should be checked. A detailed musculoskeletal examination should be done for possible fractures at at-risk sites (hips, shoulders, and spine). The patient's complaints of pain must not be assumed to be due to the vaso-occlusive pain and should not be considered too late in the diagnosis. Also, patients should be monitored in terms of other endocrine manifestations.

Acknowledgments

No funding from any pharmaceutical firm was received for this project, and the authors' time on this project was supported by their respective employers.

Competing interests

The authors declare that they have no competing interests.

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How to cite this article:
Özdemir ZT, Özkan EA, Akkoca AO, Ekim M, Börekçi E, Yıldırım T, Yaşar A. Osteoporosis and Vitamin D Deficiency in Patients with Sickle Cell Disease. J Clin Anal Med 2016;7(4): 483-7.